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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/528,644	03/20/00	THIM	L 3951.224-US

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EXAMINER	
ROMEO,D	
ART UNIT	**PAPER NUMBER**
1647	6
DATE MAILED:	07/20/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/528,644	Thim et al.
Examiner	**Art Unit**
David Romeo	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *24 May 2001*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disp sition of Claims

4) ☒ Claim(s) *27-38* is/are pending in the application.

4a) Of the above, claim(s) *34, 35, 37, and 38* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *27-33 and 36* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *27-38* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. *08/491,976*.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Claims 27-38 are pending.

2. Applicant's election of group I, claims 27-33, 36 in Paper No. 5 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 34, 35, 37, 38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 5. Claims 27-33, 36 are being examined.

4. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

5. The application is not fully in compliance the sequence rules, 37 C.F.R. § 1.821-1.825. The specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. An amino acid sequence is disclosed in Figure 2 and at page 13, line 28,

without the appropriate sequence identifier, i.e. SEQ ID NO:. Applicant may bring Figure 2 into compliance by amending either the Figure or the "Brief Description of the Drawings" to recite the appropriate sequence identifier. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. For example, language such as "residues 14 to 243 of SEQ ID NO:23" is permissible and the fragment need not be separately presented in the "Sequence Listing."

Correction is required.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claim 27 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The product as claimed reads on a product of nature. Tomasetto (2, cited by Applicants) teach that hSP has an N-terminal presumptive signal sequence (paragraph bridging pages 407-408; Figures 2 and 5), indicating that it is a secreted polypeptide. Alberts (u6)[1] teaches that most of the soluble proteins that are secreted are glycoproteins (page 589,

[1]Citations by the xaminer are in an alphanumeric format, such as "(a1)", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to

penultimate paragraph). It is therefore reasonable to assume that hSP as it occurs in nature is in glycosylated form. It is suggested that the claim 27 recite an "isolated" human spasmolytic peptide.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 27-33, 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant specification defines human spasmolytic polypeptide (hSP) as having the amino acid sequence of SEQ ID NO:1 or a functionally equivalent homologue thereof (paragraph bridging pages 2-3). The specification intends the term "homologue" to indicate a polypeptide encoded by a DNA that hybridizes to the DNA coding for hSP under conditions of high or low stringency (page 3, full paragraph 1). The specification defines the term "functionally equivalent" to indicate that the homologous polypeptide has a biological activity

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which the Notice of References Cited, PTO-892, is attached.

corresponding to that of native hSP (page 3, full paragraph 1). The claims are genus claims directed to essentially any and all glycosylated hSPs. A polypeptide encoded by a DNA that hybridizes to the DNA coding for hSP encompasses polypeptides having numerous amino acid substitutions, deletions, insertions and/or additions. The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus other than glycosylation. The specification and claims do not place any significant structural limitations on the claimed hSP other than the site and/or extent of glycosylation. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant. The specification and claims do not provide any guidance as to what changes can or should be made in order to obtain a hSP. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the term human hSP alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 28 is indefinite over the recitation of "Asn 15" because it is unclear if, for example, the fifteenth Asn out of a total of 15 or more asparagines, or the fifteenth residue from the N-terminus is intended. The metes and bounds of the claim(s) are not clearly set forth.

b. Claim(s) 27-33, 36 are indefinite because they recite the term "human spasmolytic polypeptide" and/or "hSP". Because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "spasmolytic polypeptide" and/or "hSP" an artisan cannot determine what additional limitations are placed upon a claim by the presence of this term. It is suggested that the claims recite "polypeptide" instead.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 27-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Onda (n6) in view of Tomasetto (2, cited by Applicants), Alberts (u6), Hitzeman (x6), and Lodish (w6).

Onda discloses the expression and secretion of a recombinant human polypeptide in yeast cells (page 4, line 55; sentence bridging pages 4-5; page 5, lines 8-9 and 31-34; Example 5, pages 9-10). Onda's polypeptide has high homology with pancreatic spasmolytic polypeptide (PSP) (page 6, full paragraph 3). Recombinant expression of Onda's polypeptide has the advantage of providing a large amount of the polypeptide (page 6, full paragraph 2). Onda does not teach a glycosylated hSP, as recited in claim 27, or any of the particular glycosylated forms of hSP that are recited in claims 28-33.

The instant specification defines human spasmolytic polypeptide (hSP) as having the amino acid sequence of SEQ ID NO:1 (paragraph bridging pages 2-3). Tomasetto discloses the cDNA and deduced amino acid sequence of a human spasmolytic polypeptide (hSP) (paragraph bridging pages 409-410; Figure 5). The encoded protein contains a putative signal sequence, amino acids 1-24 (Figure 5). The amino acid sequence of the encoded protein minus the putative signal peptide is identical to Applicants' SEQ ID NO:1, as indicated below:

```
RESULT    1
ENTRY             S12371      #type fragment
TITLE             spasmolytic protein 1 precursor - human (fragment)
ALTERNATE_NAMES   trefoil factor 2
ORGANISM          #formal_name Homo sapiens #common_name man
DATE              21-Nov-1993 #sequence_revision 24-May-1996 #text_change
                    18-Sep-1998
ACCESSIONS        S12371
REFERENCE         S12371
   #authors       Tomasetto, C.; Rio, M.C.; Gautier, C.; Wolf, C.; Hareuveni,
                    M.; Chambon, P.; Lathe, R.
   #journal       EMBO J. (1990) 9:407-414
   #title         hSP, the domain-duplicated homolog of pS2 protein, is
                    co-expressed with pS2 in stomach but not in breast
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                carcinoma.
   #cross-references MUID:90151615
   #accession    S12371
      ##molecule_type mRNA
      ##residues      1-130 ##label TOM
      ##cross-references EMBL:X51698; NID:g36558; PID:g36559
GENETICS
   #gene         GDB:TFF2; SML1
      ##cross-references GDB:128989; OMIM:182590
   #map_position 21q22.3
FUNCTION
   #description  inhibits gastrointestinal motility and gastric acid secretion
CLASSIFICATION   #superfamily spasmolytic protein; trefoil homology
KEYWORDS         duplication; hormone; pancreas
FEATURE
   1-24              #domain signal sequence (fragment) #status predicted
                       #label SIG\
   25-130            #product spasmolytic protein #status predicted #label
                       MAT\
   32-73             #domain trefoil homology #label TRF1\
   82-122            #domain trefoil homology #label TRF2\
   30-128,32-59,43-58,
   53-70,82-108,
   92-107,102-119    #disulfide_bonds #status predicted
SUMMARY          #length 130  #checksum 8997

  Query Match          100.0%;  Score 857;  DB 1;  Length 130;
  Best Local Similarity 100.0%;  Pred. No. 6.82e-177;
  Matches   106;  Conservative    0;  Mismatches   0;  Indels   0;  Gaps   0;

Db     25 EKPSPCQCSRLSPHNRTNCGFPGITSDQCFDNGCCFDSSVTGVPWCFHPLPKQESDQCVM 84
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy      1 EKPSPCQCSRLSPHNRTNCGFPGITSDQCFDNGCCFDSSVTGVPWCFHPLPKQESDQCVM 60

Db     85 EVSDRRNCGYPGISPEECASRKCCFSNFIFEVPWCFFPNSVEDCHY 130
           |||||||||||||||||||||||||||||||||||||||||||||
Qy     61 EVSDRRNCGYPGISPEECASRKCCFSNFIFEVPWCFFPNSVEDCHY 106
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The protein encoded by Tomasetto's cDNA also contains a classic N-linked glycosylation site at amino acid residues 39-41, which is the amino acid sequence Asn-X-Ser/Thr wherein X is any amino acid. Amino acid residues 39-41 of the protein encoded by Tomasetto's cDNA correspond to amino acids 15-17 of Applicants' SEQ ID NO:1. Tomasetto discloses strong conservation of primary structure between PSP, mSP and hSP which suggest that these three proteins fulfill similar biological functions (page 412, column 2, full paragraph 4). Tomasetto

does not teach a glycosylated hSP, as recited in claim 27, or any of the particular glycosylated forms of hSP that are recited in claims 28-33.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to express PSP in yeast cells, as taught by Onda, and to modify that teaching by expressing hSP, as taught by Tomasetto, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings because recombinant expression of hSP in yeast cells would have the advantage of providing a large amount of readily purified hSP.

Alberts, Hitzeman, and Lodish are cited as evidence of what was in the public's possession before applicant's invention.

Alberts teaches that most of the soluble proteins that are secreted are glycoproteins (page 589, penultimate paragraph).

Hitzeman teaches N-linked glycosylation at the amino acid sequence Asn-X-Ser/Thr wherein X is any amino acid (page 436, full paragraph 2).

Lodish teaches that most secreted proteins are glycosylated (page 699, column 2, full paragraph 3), that in all N-linked oligosaccharides N-acetylglucosamine is linked to Asn (page 700, column 1, first full sentence), that N-linked oligosaccharides always contain mannose as well as N-acetylglucosamine (page 700, column 1, third sentence), and that N-linked oligosaccharides can have as many as 60 mannose residues in yeast (page 701, legend to Figure 16-27).

Expression of hSP in yeast cells would result in secretion of hSP because it comprises a putative signal peptide. Most secreted proteins are glycosylated. Therefore, expression and secretion of hSP in yeast cells would achieve the invention of claim 27. Furthermore, expression and secretion of hSP in yeast cells would achieve the invention of claims 28-33 because Asn 15 of hSP is a classic N-linked glycosylation site, in all N-linked oligosaccharides N-acetylglucosamine is linked to Asn, N-linked oligosaccharides always contain mannose as well as N-acetylglucosamine, and N-linked oligosaccharides can have as many as 60 mannose residues in yeast. The invention is prima facie obvious over the prior art.

14. Claims 27, 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Onda (n6) in view of Tomasetto (2, cited by Applicants), Alberts (u6), Hitzeman (x6), and Lodish (w6) as applied to claim 27 above and further in view of Turco (v6). Onda in view of Tomasetto, Alberts, Hitzeman, and Lodish teach a glycosylated hSP, as discussed above. Onda in view of Tomasetto, Alberts, Hitzeman, and Lodish do not teach a pharmaceutical composition comprising a glycosylated hSP together with a pharmaceutically acceptable carrier or excipient. Turco teaches that proper electrolyte concentration and balance in plasma and tissues are critical for proper body function and that the electrolytes in normal saline more closely approximate the composition of the extracellular fluid than solutions of any other single salt (page 1570, column 2, bottom). Turco does not teach a pharmaceutical composition comprising a glycosylated hSP together with

a pharmaceutically acceptable carrier or excipient. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a glycosylated hSP, as taught by Onda in view of Tomasetto, Alberts, Hitzeman, and Lodish, and to modify that teaching by making a pharmaceutical composition comprising a glycosylated hSP together with normal saline, as taught by Turco, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings for the purpose of pharmacologic screening of a glycosylated hSP and because electrolytes in normal saline more closely approximate the composition of the extracellular fluid than solutions of any other single salt. The invention is prima facie obvious over the prior art.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

a timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. a terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 27-33, 36 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 10-13 of U.S. Patent No. 5,783,416 (a6). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are generic to and fully encompass the claims of the patent.

Conclusion

17. No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

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ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

JULY 19, 2001

BRS	L1	977	spasmolytic	USPAT	7/19/01 12:26			0
BRS	L2	39	spasmolytic with human	USPAT	7/19/01 12:26			0
BRS	L3	7	spasmolytic near3 (peptide$1 or polypeptide$1)	USPAT	7/19/01 12:27			0